IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant	:	Weinberg	
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Examiner	:	Kishore, Gollamudi	
For	:	LIPID EMULSIONS IN THE TREATMENT OF SYSTEMIC POISONING	
Docket No.	:	69-06	
Customer No.	:	23713	

DECLARATION OF GUY WEINBERG UNDER 37 C.F.R. 1.132

I Guy Weinberg declare that;

I am a co-inventor of the above-referenced application. I am a full professor of Anesthesiology at the University of Illinois at Chicago College of Medicine, Associate Department Head, and Director of Research for Anesthesiology. I am board certified in Internal Medicine (1979), Medical Genetics (1981) and Anesthesiology (1986). I am a member of the Association of University Anesthesiologists.

The invention was exemplified in the specification by showing that lipid emulsion infusion aids resuscitation from bupivacaine-induced asystole in rats. Bupivacaine is a local anesthetic which can induce severe cardiotoxicity. We have subsequently demonstrated that lipid infusion also reversed bupivacaine toxicity in dogs receiving an otherwise fatal overdose, as reported in Weinberg G, Ripper R, Feinstein DL, Hoffman W. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. Reg Anesth Pain Med (2003)28:198-202, Exhibit A.) These data validate in a canine model the earlier findings in rat models of local anesthetic toxicity showing the efficacy of lipid infusion in severe bupivacaine toxicity.

Ropivacaine, prilocaine and mepivacaine are other local anesthetics which can induce severe cardiotoxicity. I have recently been contacted by Dr. Rainer Litz, an

Anesthesiologist from Dresden, Germany who reported to me three instances in which he employed lipid emulsion to treat severe toxicity induced by these anesthetics. These cases have not as yet been reported in the medical literature. In a first case, Dr. Litz indicated that in 1999 a small (50kg) patient received a brachial plexus block with ropivacaine 400 mg and shortly thereafter developed cardiovascular collapse. Dr. Litz indicated that the patient was unresponsive to standard resuscitation methods and drugs until he recommended using lipid infusion. The patient received 100 mL of 20% lipid emulsion and very quickly regained normal blood pressure and heart rate. The patient recovered uneventfully without neurological deficit. This report confirms the efficacy of lipid infusion in treating overdose and cardiovascular collapse due to ropivacaine, an anesthetic other than bupivacaine.

In a second case, Dr. Litz reported to me that a patient had a supraclavicular brachial plexus block with a combination of prilocaine and mepivacaine. After a few minutes, the patient complained of dizziness and drowsiness, did not respond to verbal commands and developed ventricular extrasystoles. The patient then received 250 ml of 20% Intralipid. Within 10 min the patient regained consciousness, responded to verbal commands and the extrasystoles disappeared. Blood draws before and after lipid therapy showed: Prilocaine prior to lipid infusion 0.92 µg/ml afterwards 0.35µg/ml Mepivacaine 4.08 µg/ml , after lipids 2.30µg/ml. This second report indicates that lipid can reduce plasma local anesthetic concentration and further confirms its efficacy in treating toxicity of local anesthetics other than bupivacaine, here a combination of mepivacaine and prilocaine. It also shows efficacy in treating symptoms and signs other than cardiac toxicity, in this case, altered mental status.

In a third case, a patient with combined psoas compartment block and sciatic nerve block for total knee joint replacement received a total dose of 400 mg of mepivacaine and 200 mg of ropivacaine for both blocks. About 15 min following the last dose, the patient became agitated, complained of dizziness and lost consciousness. Local anesthetic toxicity (absorption) was suspected, the patient received oxygen by mask and lipid infusion was started. The patient did not develop seizures and became

responsive to verbal commands within 10 min patient after starting lipids. Under these circumstances, the patient would have been expected to progress to seizure and cardiovascular collapse without effective intervention. This case indicates that the preemptive treatment with lipid emulsion prevented progression from symptomatic prodrome to potentially fatal toxicity.

I personally supervised the resuscitation of a patient who experienced sudden cardiovascular collapse after a peripheral nerve block with 600 mg mepivacaine. Notably, the patient's preoperative cardiac output was low and the ejection fraction was 10%. Standard resuscitation by ACLS protocol failed to alter the underlying rhythm of asystole with intermittent ventricular fibrillation. After 20 minutes of unsuccessful ACLS, including multiple rounds of shocks and drugs, the patient was given 20% intralipid: two bolus injections of 1 mL/kg and continuous infusion (0.25 mL/kg/min). The patient's ECG quickly normalized to sinus tachycardia and blood pressure returned to 170/80. Vital signs were stable for 30 minutes. Unfortunately, during transfer to the ICU, the lipid infusion was discontinued and the patient suffered another cardiac arrest from which he did not recover, despite continued ACLS and lipid infusion. This case, however, confirms that lipid infusion is effective in reversing cardiac arrest from mepivacaine. It further suggests that maintaining a continuous infusion is important to successful resuscitation.

Cocaine is also a local anesthetic that can induce severe cardiotoxicity. Cocaine toxicity is, however, a much broader medical problem and comprises a large fraction of drug-related emergency room visits and deaths in the US. It has been estimated that more than 10% of the U.S. population has used cocaine at least once. Cocaine use is accompanied by a high risk of serious adverse effects involving the cardiovascular system and at high doses, cocaine toxicity resembles bupivacaine toxicity - i.e. both produce potentially fatal malignant ventricular arrhythmias, conduction block, depressed contractility, and asystole. Because of the significant potential benefit, we have screened lipid infusion as a method for treating cocaine toxicity. We infused anesthetized, ventilated rats with lipid emulsion (20% Intralipid at 4 mL/kg for 2 minutes)

then intravenous infusion of cocaine at 10 mg/kg/min to asystole. Endpoints were reduction in blood pressure to 40 mmHg and asystole. Mean times to 40 mmHg were 143+/-22 seconds and 320+/-46 seconds for control (saline) and lipid treated animals, respectively (+/- SEM; n = 5, for both groups). For asystole, the times were 368+/-27 seconds and 602+/-38 seconds for control and lipid-treated, respectively. Unpaired t-test with Welch's correction showed that these differences were significant for both the hypotension ($p < 0.02$) and asystole ($p<0.003$) endpoints. These finding indicate that lipid infusion can be used to treat patients experiencing acute cardiovascular compromise in cocaine overdose.

I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

May 15, 2006 .....
DATE


Guy Weinberg